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<p>(21) International Application Number: PCT/HU89/00039 (22) International Filing Date: 5 August 1989 (05.08.89) (71) Applicant (for all designated States except US): VARÁNUSZ GM [HU/HU]; Serpentox Biolabor, H-2634 Nagybörzsöny (HU). (72) Inventors; and (75) Inventors/Applicants (for US only) : BODROGI, Lajos [HU/HU]; Tanácsköztársaság u. 101, H-2120 Dunakeszi (HU). PÓLUS, Péter [HU/HU]; Levél u. 28, H-2600 Vác (HU). HETÉNYI, Lászlóné [HU/HU]; Ander u. 12, H-1119 Budapest (HU). (74) Agent: BUDAPESTI NEMZETKÖZI ÜGYVÉDI MUNKAKÖZÖSSÉG; 10, Dalszínház u., H-1061 Budapest VI (HU).</p>		<p>(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent)*, DK, FI, FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent), US.  <b>Published</b> <i>With international search report.</i></p>
<p>(54) Title: PROCESS FOR PRODUCING PHARMACOSMETICS</p> <p>(57) Abstract</p> <p>The invention relates to a method of producing pharmacosmetics comprising snake-venom. The method of the invention comprises processing the - preferably lyophilized - toxin <i>Crotali atrocis</i> as active substance, in a quantity of 0,0002 - 0,1 % as compared to the total amount of the composition, into ointment, aqueous suspension, emulsive composition, gel-formed composition and the like with usual additives and/or auxiliaries.</p>		

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## PROCESS FOR PRODUCING PHARMACOSMETICS

Technical Field

The object of the invention is a process for producing pharmacosmetics comprising snake-venom.

5 Background Art

It is well known that the Soviet pharmaceutical industry produces and markets an ointment under the trade name Viprosal, the active ingredient of which is viper venom.

10 For veterinary purposes the venom of a snake belonging to Bungarus genus, of cobra (Naja genus) and of Crotalus terrificus - differing from the species Crotalus atrox - has been used. These solutions are disclosed in patent specifications GB 1 446 284, US 4 027 012, 4 126 676 and 4 292 308.

Disclosure of the Invention

15 It has been found that the venom of Crotalus atrox is a complex active substance which has analgetic, hyperaemizing and spasmolytic activity at the same time and may be used for both therapeutic and veterinary purposes. The compositions known from the literature do not dispose of such a  
20 complex and multiple activity.

The composition produced by the process of the invention comprises thus the - preferably lyophilized - venom of Crotalus atrox as active substance, in a quantity of 0,0002 to 0,1 % as compared to the total amount of the composition,  
25 processed into ointment, aqueous suspension, emulsive composition, gel-formed composition, etc., with usual additives and/or auxiliaries.

The toxin Crotali atrocis is a light yellow, odourless powder; identity: dissolved in 1 mg of water and dropped on  
30 filter-paper with ninhydrin it discolours at a slight heat effect.

Determination of contents: nitrogen content 11,5 % at least according to Ph.Hg.VII (Hungarian Pharmacopoeia).

35 The composition is for external used in case of rheumatism, arthritis, arthrosis, ischias, lumbago, muscular aches

occurring after sport achievements, and the like.

The production of the composition comprises - if processed for example as ointment - mixing methylsalicylate and camphoric acid at room temperature. The lyophilized toxin

5 Crotali atrocis is dissolved in distilled water, then mixed with methylsalicylate in a homogenizer of high speed of revolutions. The aqueous toxin solution is added dropwise, the substance is then homogenized for 4 hours at least. The suspension is added to a mass of ointment Unguenta composita

10 (a mixture of equal proportion of polyoxetene 400 and polyoxetene 1540) and is homogenized for 6 to 8 hours at room temperature. The obtained composition may be stored in dry, cool place for 5 years without decomposition.

Best Mode of Carrying out the Invention

15 The composition produced by the process of the invention is illustrated by the following non-limiting examples.

Example 1 (ointment)

The following components are mixed according to the technology described above:

20 Toxin Crotali atrocis sicc.	0,001 g
methylsalicylate	6,0 g
camphoric acid	3,0 g
Unguenta composita ad	100,0 g

Example 2 (ointment)

25 In case of tubes of 50 g 10 µg of toxin at the least, 1000 µg of toxin at the most, but preferably 50 µg of toxin are used.

The components are mixed according to the technology referred

30 to above.

In addition to the active substance, the ointment contains 5 to 20 % by mass of water and detergent may also be used.

In this case the manufacturing technology is modified,

35 i.e. the camphoric acid and methylsalicylate are mixed with

0,1-2,0 % of detergent, e.g. with Tween 20 or Na-laurylsulfate.

As additive, conserving agents, such as Sol. conservans may be added to the ointment, in a quantity of 0,1-0,5 % by mass.

Example 3

Instead of ointment, aqueous suspension is produced. In the formula of Example 1, Unguenta composita is replaced by ethyl alcohol in a concentration of 30-80 % by mass.

10 Example 4

Emulsive composition is prepared by using sunflower oil instead of Unguenta composita and shaking up before use is stipulated in the instructions for use, or sunflower oil is used only in Unguenta composita instead of polyoxetene 1540.

Example 5

Gel-formed composition is obtained if instead of polyoxetene 1540 3 % by mass of aqueous solution of hydroxymethylcellulose is used.

20 During the application for example a stick of 3-4 cm of ointment is expressed on the skin surface and massaged by fine medico-massage on the aching spot (joint) for 5-10 minutes morning and evening, for six days.

At one week intervals the treatment is repeated 3-4 times.

The ointment cannot be used on skinless surfaces.

C L A I M :

Process for producing pharmacosmetics comprising  
snake-venom, c h a r a c t e r i z e d i n t h a t t h e  
5 - preferably lyophilized - toxin *Crotali atrocis* is pro-  
cessed as active substance, in a quantity of 0,0002 - 0,1 %  
as compared to the total amount of the composition, into  
ointment, aqueous suspension, emulsive composition, gel-  
-formed composition and the like with usual additives  
10 and/or auxiliaries.

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# INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 89/00039

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) * According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. <sup>5</sup> A 61 K 35/58		
<b>II. FIELDS SEARCHED</b> Minimum Documentation Searched * Classification System   Classification Symbols IPC <sup>5</sup>   A 61 K 35/00, 35/56, 35/58, 39/38 Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of Document, ** with Indication, where appropriate, of the relevant passages **	Relevant to Claim No. **
X	DE, A1, 3 639 796 (ONCOGEN), 09 July 1987 (09.07.87), see page 2, line 66 - page 3, line 4; page 6, lines 1-51. -----	(1)
* Special categories of cited documents: ** "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "Z" document member of the same patent family		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search 05 April 1990 (05.04.90)		Date of Mailing of this International Search Report 18 April 1990 (18.04.90)
International Searching Authority AUSTRIAN PATENT OFFICE		Signature of Authorized Officer 

Anhang zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentedokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

Annex to the International Search Report on International Patent Application No.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned International search report. The Austrian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Annexe au rapport de recherche internationale relatif à la demande de brevet international n°.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche internationale visé ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office autrichien des brevets.

Im Recherchenbericht angeführtes Patent- dokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
DE-A1- 3637796	09-07-87	AU-A1-65563/86	28-05-87
		AU-A1-65609/86	28-05-87
		BE-A1- 905790	19-05-87
		CH-A - 670451	15-06-89
		CN-A -66108597	30-09-87
		DK-A0- 5609/86	21-11-86
		DK-A - 5609/86	23-05-87
		ES-AF- 2002913	01-10-88
		FI-A0- 864715	19-11-86
		FI-A - 864715	23-05-87
		FR-A1- 2590576	29-05-87
		GB-A0- 8627710	17-12-86
		GB-A1- 2185020	08-07-87
		LU-A - 86663	26-06-87
		NL-A - 8602939	16-06-87
		PT-A - 83790	01-12-86
		SE-A0- 8604991	21-11-86
		SE-A - 8604991	23-05-87
		US-A - 4731439	15-03-88
		US-A - 4774318	27-09-88
		YU-A - 1995/86	30-06-88
		ZA-A - 8608849	29-07-87
		JP-A2- 1131196	24-05-89
		JP-A2- 1131196	24-05-89